39. (Once amended) The chimeric molecule of claim 34, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 of at least 10 [:]mM.

43. (Once amended) The chimeric molecule of claim 34, wherein said antibody [has]comprises the amino acid sequence of SEQ ID NO: 1.

44. (Once amended) The chimeric molecule of claim 34, wherein said antibody [has]comprises the amino acid sequence of SEQ ID NO: 2.

53. (Once amended) A [pharmaceutical] composition comprising a pharmacological excipient and the antibody of claims 1 or 16

54. (Once amended) A [pharmaceutical] composition comprising a pharmacological excipient and the chimeric molecule of claim 34.

REMARKS

Status.

Claims 1, 3-22, 34-44, and 53-54 are pending with entry of this amendment, claims 2, 23-33, and 45-52 being cancelled and no claims being added herein. Claims 1, 4, 12, 13, 14, 15, 16, 17, 21, 22, 39, 43, 44, 53, and 54 are amended herein. These amendments introduce no new matter. Support for the amendments is replete throughout the specification. For example, support for the amendment to claim 1 is found at page 34, lines 25-32, and in claim 2 as filed. The remaining claims are amended to correct typographical errors, to clarify that "has" is open claim language, and to delete the word "pharmaceutical".

Claims 1-22, 34-44, and 53-54 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-13, 16-20, 34-42, and 53-54 were rejected under 35 U.S.C. §112, first paragraph. Claims 1-22, 34-44, and 53-54 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Maier, *et al.* (1991) *Cancer Res.*, 51: 5361-5369. Applicants respectfully traverse these rejections by argument and amendment as explained below.

Address Correction.

Applicants note that the November 8, 1999 Office Action was incorrectly mailed to Townsend and Townsend and Crew, Two Embarcadero Center, 8th Fl. San Francisco, CA 94111.

A Power of Attorney was filed on June 10, 1999 containing a bar code sticker bearing the present firm's customer number **(020227)**. It is Applicant's understanding that the use of this customer number should have effected a correction of mailing address to the present firm. As this has not occurred, Applicants hereby request that future mailings with respect to this application be directed to:

Majestic, Parsons, Siebert & Hsue
Four Embarcadero Center, Suite 1100
San Francisco, CA 94111-4106

Amendment of July 10, 1999.

Applicant note that the amendment to page 20, line 25 of the specification, filed 6/10/99 was note entered because the text was not found at that position. Applicants do not understand the Examiner's difficulty. Applicant's copy clearly shows the word "herein" in that line as stated in the amendment. Nevertheless, for convenience, Applicant's provide the same amendment in more detail above.

Restriction requirement made final.

Applicants note the restriction requirement made final. Accordingly, non-elected claims 23-33, and 45-52 are cancelled herein. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled and amended out subject matter and the claim cancellations and amendments should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Oath/Declaration.

The Examiner alleged that the Oath/Declaration was defective because it allegedly did not state that the person making the oath or declaration has reviewed and understands the contents of the specification.

Applicants note that the Declaration at page 1, paragraph number 2 expressly states:

> 2. I believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is ought in the patent application entitled "INTERNALIZING ErbB2 ANTIBODIES, "Serial No. 09/350,056, filed February 12, 1999, and **I have reviewed and understand the contents of the specification including its claims.** [emphasis added]

In view of the above-quoted language present in the Declaration, Applicants submit the Declaration **is not** defective and no substitute Declaration is required.

Information Disclosure Statement.

Applicants note with appreciation that the references cited in the IDS filed 9/23/99 and 7/26/99 have been thoroughly considered. Applicants note that the Examiner crossed out references B6, B7, B8, and C40 which recited international search reports for PCT applications arguing that "it is not clear that international search reports are publicly available".

Applicants respectfully disagree. It is well known that international search reports are published and generally available from the same sources that provide PCT publications. Accordingly, Applicants respectfully request that the search reports (B6, B7, B8, and C40) be made of record and appear on the face of the patent.

Objections to the specification

The specification was objected to for a number of spelling/typographical errors. These have been corrected with entry of this amendment thereby obviating this objection.

The present status of all copending applications cited in the specification is unchanged at this time and need not be updated.

Sequence Requirements.

The Examiner noted that the application contains sequence disclosures on page 40, line 22 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §§1.821(a)(1) and (a)(2) and further alleged that the application fails to comply with the sequence listing rules "for reason(s) set forth on the attached Notice TO Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants note that no Notice To Comply was attached to the Office Action. Moreover, page 1 of the Office Action, under attachments, does not indicate that such a Notice was attached.

Nevertheless, Applicants observe that the short peptide sequences on page 40 are not in the sequence listing. Accordingly, in accordance with 37 C.F.R. §§1.821-1.825, Applicants submit herewith the required paper copy and computer readable copy of the Substitute Sequence Listing. The substitute listing incorporates the sequences on page 40 as SEQ ID NOS:5-8.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" (Version 2.0) and is identical to that of the paper copy.

35 U.S.C. §112, Second Paragraph.

Claims 1-22, 34-44, and 53-54 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for a variety of reasons as explained below:

A) Use of "F5" and "C1".

Claims 1-11, 14-15, 21-22, 34, and 53-54 were rejected as allegedly indefinite for reciting "F5 and C1" because "other laboratories/inventors may use the same laboratory designation to refer to different antibodies." Per the Examiner's recommendation, claim 1 is amended to recite " F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2)" thereby obviating this rejection.

B) Use of "10:M" binding affinity.

Claims 4, 17, and 39 were rejected as allegedly indefinite for reciting "-erb on cells of at least '10M' or '"10:M"'. Claims 4, 17, and 39 are amended with entry of this amendment to recite "c-erbB2 of at least 10 M" thereby obviating this rejection.

C) Recitation of "-erbB2".

Claims 4 and 39 were rejected as allegedly indefinite for reciting "-erbB2". AS recognized by the Examiner this is a typographical error corrected to "c-erbB2" with entry of this amendment.

D) Recitation of "said antibody" in claim 16.

Claims 16-20, 34-44, and 53-54 were rejected as allegedly indefinite for reciting "said antibody" in claim 16, line 7. According to the Examiner it is unclear whether "said antibody" refers to the antibody of line 1 or to the anti-idiotypic antibody of line 5. Claim 16 is amended to eliminate this confusion thereby obviating this rejection.

E) Recitation of "least" in claim 16.

Claim 16 was rejected as allegedly indefinite for reciting "comprising least" as it was allegedly unclear whether "least" or "at least" was intended. Claim 16 is amended herein to recite "at least" thereby obviating this rejection.

F) Recitation of "polypeptide sequence" in claim 16.

Claim 16 was rejected as allegedly indefinite for reciting "polypeptide sequence". According to the Examiner the term "sequence" in this context refers to information describing a nucleic acid or amino acid sequence and not to the molecule itself. Claim 16 is amended herein to recite "a polypeptide comprising an amino acid sequence" thereby obviating this rejection.

G) Recitation of "pharmaceutical composition" in claims 53 and 54.

Claims 53 and 54 were rejected as allegedly indefinite in the recitation of a "pharmaceutical composition". Claims 53 and 54 are amended herein to delete the word "pharmaceutical" from the preamble thereby obviating this rejection.

H) Dependencies of claims 20 and 21.

Claims 20 and 21 were rejected as allegedly indefinite because it was allegedly unclear if they are a duplication of claims 14 or 15 or if they are dependent on claim 16. Claims 20 and 21 are amended herein to correct their dependency to claim 16 thereby obviating this rejection.

I) Recitation of "has".

Claims 12-15, 21, 22, 43, and 44 were rejected as allegedly indefinite for recitation of the term "has". The Examiner alleged that it was unclear whether "has" is "open" or "closed" claim language. Claims 12-15, 21, 22, 43, and 44 are amended herein to replace "has" with "comprises" thereby obviating this rejection.

J) Doctrine of equivalents.

The amendments described in sections (A) through (I) above are made solely to address issues of claim clarity under 35 U.S.C. §112, second paragraph, and not to address rejections in light of prior art. Applicants expressly state for the record that these amendments do not preclude the use of the Doctrine of Equivalents as applied by an appropriate court. Applicants are clearly entitled, absent amendments in view of the prior art, to assert claims issue from this application against infringers under the Doctrine of Equivalents (*see, e.g. Warner-Jenkinson Co. v Hilton Davis Chem.* 41 USPQ2d 1865 (1997), *Litton Systems Inc. v Honeywell* Inc. 46 USQ2d 1341 (Fed. Cir. 1998)).

In view of the foregoing, Applicants believe the rejections under 35 U.S.C. §112, second paragraph, are overcome and respectfully request that they be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 1-13, 16-20, 34-42, and 53-54 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly is not enabling for all antibodies that specifically bind to the c-erbB2 receptor epitope and

1) have conservative substitutions;
2) share at least 70% sequence identity to SEQ ID NOS: 1 or 2;
3) differ from SEQ ID NOS: 1 or 2 by no more than 30 residues;

4) that comprise at least 10 contiguous amino acids from SEQ ID NOS: 1 or 2 and that do not contain six CDRs.

In particular the Examiner argued that the F5 and C1 epitope(s) are not characterized that defining epitopes is difficult, that recognition of carbohydrate moieties by antibodies is a complex and unpredictable task. The Examiner further argued that even if one were able to identify the region of c-erbB2 that bound F5 or C1, the precise epitope would still be indeterminate.

The Examiner also argued that CDR grafting is unpredictable, that "70% sequence identity has no meaning in the art. The Examiner concluded that the specification "provides inadequate direction of guidance regarding how to produce the antibodies as broadly defined by the claims as well as the epitope the antibodies bind to in order to produce the claimed antibodies." He further concluded that taken in view of the unpredictability of the art undue experimentation would be required to make and use the invention commensurate with the scope of the claims. Applicants respectfully traverse by amendment and argument.

The Examiner is reminded that to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive

Indeed, **the Federal Circuit has expressly stated that simple screening, in particular screening of antibodies, is not undue experimentation**:

> Enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "[T]he key word is 'undue' not 'experimentation'. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the

art; (7) predictability of the art; and (8) breadth of the claims. *Wands citing Ex parte Forman Inc.,* 230 USPQ 546 (BPAI 1986).

A) Enablement does not require identification of the F5 or C1 epitope(s).

Claim 1, as amended herein, eliminates the reference to an epitope bound by F5 or C1 and instead states that the antibody

> [I]s cross reactive with F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) at c-erbB2, and that is an internalizing antibody.

Determination of antibody cross-reactivity at a particular target is routine to those of skill in the art. Detailed descriptions of methods of determining such cross-reactivity are provided in the specification at pages 32 - 35. Moreover, such determinations are essentially no more complex than hybridoma screening **which the Federal Circuit has already determined is not undue experimentation**.

In view of the fact that the claims, particularly as amended herein, do not require determination of the F5 or C1 antibody, the Examiner's comments about the difficulty and unpredictability in determining a particular epitope are moot.

B) The "Forman/Wands Factors" weigh in favor of patentability.

A review of the specification in light of the "Forman Factors "discussed above and by the Examiner indicates that the claimed single chain antibodies can be produced without undue experimentation. The specification provides detailed examples describing production of single chain antibodies in accordance with the claims (Factor 3). Moreover, F5 and C1 antibodies are not characterized simply by binding specificity and avidity, but actual amino acid sequences are provided affording the practitioner considerable guidance as to the production of the claimed invention (Factor 2).

Contrary to the Examiner's assertion, relatively little experimentation is necessary (Factor 1). Using phage display technology as described in the application, literally millions of single chain antibodies can be expressed and screened in a single experiment. Moreover the Examiner is respectfully reminded that the Court of Appeals of the Federal Circuit has already held that antibody screening is not undue experimentation (*In re Wands*).

The Examiner is also reminded that by using phage display technology, as described in the specification, to screen literally millions of antibodies in a single experiment and to progressively enrich a library of antibodies having the desired characteristics, the identification of suitable antibodies that differ by a few amino acid substitutions (*e.g.* conservative mutations) is routine. Thus, assuming *arguendo*, that *a priori* prediction of the effect of any particular mutation is difficult **such *a priori* prediction is not required by the present invention**. As shown by the examples presented in the specification, the art is extremely predictable with respect to the ability to obtain such antibodies with only routine experimentation (Factor 7).

The state of the prior art (antibody production and phage display technology) is extremely well developed (Factor 5), the invention is well characterized/defined (Factor 4), and the claims are relatively narrow being limited to internalizing single chain antibodies cross reactive with F5 and C1 at c-erbB2 (Factor 8). Moreover, the relative skill of those in the art is extremely high (*e.g.* Ph.D.). The Forman/Wands factors when considered as a whole clearly indicate that production of antibodies in accordance with the claims does not require undue experimentation. Accordingly the rejections under 35 U.S.C. §112, first paragraph, should be withdrawn.

C) Applicants have demonstrated effective CDR shuffling.

With respect to the Examiner's comments regarding the production of antibodies having different CDRs than those exemplified in the F5 and C1 listings, Applicants note that the Examples illustrate both mutagenesis techniques and CDR shuffling techniques that produce single chain antibodies having improved avidity and/or specificity. Applying such techniques and screening the resulting libraries in competition with F5 or C1 requires only routine experimentation. Thus, identification/production of antibodies comprising only 1, 2, 3, 4, or 5 of the CDRs shown in the sequence listings (*e.g.* the remaining CDRs being "new" shuffled into the antibody) is not undue experimentation.

D) Determination of sequence identity is routine.

The Examiner's comments regarding sequence identity are not the proper basis of a 35 U.S.C. §112, first paragraph, rejection. Determination of sequence identity is routine to

those of skill in the art. Moreover, a number of commercially available software packages and/or web sites (*see, e.g.* www.sequenceanalysis.com) are easily used to calculate sequence identity. In addition, the specification expressly identifies suitable algorithms, the reference publications, the scoring matrix (in the case of BLAST), and suitable parameters. There is simply no question that the specification teaches one of ordinary skill in the art how to calculate the recited 70% sequence identity and the rejection on this basis under 35 U.S.C. §112, first paragraph, should be withdrawn.

If the Examiner wishes to make this rejection under 35 U.S.C. §112, second paragraph, arguing that the claim is indefinite because it doesn't expressly recite the algorithm, Applicants would consider identifying the appropriate algorithm in the claim.

E) Doctrine of equivalents.

The amendment of claim 1 described in section (A), above, was made solely to address issues under 35 U.S.C. §112, second paragraph, and not to address rejections in light of prior art. Applicants expressly state for the record that these amendments do not preclude the use of the Doctrine of Equivalents as applied by an appropriate court. Applicants are clearly entitled, absent amendments in view of the prior art, to assert claims issue from this application against infringers under the Doctrine of Equivalents (*see, e.g. Warner-Jenkinson Co. v Hilton Davis Chem.* 41 USPQ2d 1865 (1997), *Litton Systems Inc. v Honeywell* Inc. 46 USQ2d 1341 (Fed. Cir. 1998)).

In view of the foregoing, Applicants submit the Examiner has failed to make his *prima facie* case under 35 U.S.C. §112, first paragraph, and the rejections on these grounds should be withdrawn.

35 U.S.C. §112, first paragraph, Biological Deposit.

Claims 1-13, 16-20, 34-42, and 53-54 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description. Applicants respectfully traverse.

The specification provides both amino acid sequences and nucleotide sequences for F5 and C1 single chain antibodies. Using this information, the antibodies or CDRs comprising the antibodies can be chemically synthesized or recombinantly expressed according to standard methods well known to those of skill in the art.

In addition, the examples provide detailed descriptions for the production of human single chain antibody libraries into which the F5 or C1 antibodies or CDRs can routinely be incorporated. Phage display techniques are well known to those of skill in the art, and detailed protocols are provided in the specification. Applicants have met the 35 U.S.C. §112, first paragraph, requirement and no biological deposit is required.

35 U.S.C. §102.

Claims 1-22, 34-44, and 53-54 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Maier, *et al.* (1991) *Cancer Res.*, 51: 5361-5369. Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). In the instant case, claims 1 and 16 are amended to recite a "**single chain antibody**." In contrast, Maier *et al.* discloses the use of **complete monoclonal antibodies**. The specification at page 5362 expressly states that:

> **Hybridomas that produced the murine monoclonal antibodies** TA1 (IgG1) and OD3 (IgM) . . . were obtained form Applied biotechnology (Cambridge, MA). **Three other murine monoclonal antibodies** MPOC21 (IgG1), 454A12 (IgG1), and 9C6 (IgM) were obtained from Cetus Corporation (Emeryville, CA). [emphasis added]

Maier *et al.* **does not disclose or otherwise teach or suggest a single chain antibody.** Maier *et al.* thus fails to provide limitation of the claimed invention and therefore **does not anticipate** claims 1-22, 34-44, and 53-54 as amended. Accordingly, the rejection under 35 U.S.C. §102(b) should be withdrawn.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 248-5500.

Dated: May 8, 2000.

Respectfully submitted,

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Atty. Docket: 2500.116US3

Encl: 1) Petition for 3 month extension of time.
2) Sequence listing paper copy and CRF.

File: C:_docs\2500 UC OTT\116US3\2500.116US3 amend 1.doc